660045

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **COLETICA**, the applicant/Nominated Person in respect of Application No. 24745/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY FIFTH day of MARCH 1994

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1650543)

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(54) Title
UTILISATION OF CROSS-LINKED COLLAGEN FOR THE FABRICATION OF A STITCHABLE, BIOCOMPATIBLE, SLOW RESORPTION MEMBRANE

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(56) Prior Art Documents
AU 33467/93 31/00 D04H 13/00
US 5028965
US 4600533

(57) Claim

1. Use of collagen crosslinked with a crosslinking agent for the manufacture of a suturable, biocompatible slow-resorbing membrane, preferably for guided tissue regeneration, said membrane either comprising crosslinked collagen from a starting collagen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

8. A suturable, biocompatible slow-resorbing membrane, preferably for guided tissue regeneration comprising collagen crosslinked with a crosslinking agent, said membrane either comprising a crosslinked collagen from a starting collagen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

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14. A process for the coagulation of collagen for the preparation of coagulated collagen according to any one of claims 1 to 7, which comprises coagulating a collagen gel with a coagulating agent comprising an ammoniacal solution.

24745/92

ANNOUNCEMENT OF THE LATER PUBLICATION OF AMENDED CLAIMS
(AND, WHERE APPLICABLE, STATEMENT UNDER ARTICLE 19)

PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
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(54) Title: UTILISATION OF CROSS-LINKED COLLAGEN FOR THE FABRICATION OF A STITCHABLE, BIOCOMPATIBLE, SLOW RESORPTION MEMBRANE

(54) Titre: UTILISATION DE COLLAGENE RETICULE POUR LA FABRICATION D'UNE MEMBRANE SUTURABLE, BIOCOMPATIBLE A RESORPTION LENTE

(57) Abstract

The invention relates to the utilization of cross-linked collagen for the fabrication of a stitchable, biocompatible, slow resorption membrane. The collagen used, may be native collagen particularly of type I or type III, atelocollagen or a mixture of collagen or atelocollagen with glycosaminoglycan. Said membrane is stitchable, biocompatible and slow resorbing, thereby enabling its use for guided tissue regeneration.

(57) Abrégé

L'invention concerne l'utilisation de collagène réticulé pour la fabrication d'une membrane suturable, biocompatible à résorption lente. Comme collagène, il peut s'agir de collagène natif en particulier de type I ou de type III, d'atélocollagène ou un mélange de collagène ou d'atélocollagène avec un glycosaminoglycanne. Cette membrane est suturable, biocompatible et à résorption lente, ce qui permet de l'utiliser pour réaliser une régénération tissulaire guidée.

The invention relates essentially to the use of collagen crosslinked with a crosslinking agent for the manufacture of a suturable, biocompatible slow-resorbing membrane, and to such a membrane. Such a membrane can advantageously be used for guided tissue regeneration.

The concept of guided tissue regeneration was recently developed by Nieman and in practice involves the use of a biocompatible material capable of separating two cell populations *in vivo*.

The principle is as follows:

When an empty space is created in a living tissue, it is filled by the most rapidly multiplying cell line adjacent to this void, unless access is deliberately limited to a single cell type, which will then be the only one to colonize the void to be filled.

This principle is utilized in guided tissue regeneration for directing the repair of damaged tissues in the manner desired by the clinician.

Thus, for example, in the case of periodontology, it is very difficult to repair damaged periradicular ligamentous tissue. In fact, during the periodontium healing processes, the epithelium regenerates more rapidly than the ligament and tends to take its place.

The guided tissue regeneration technique used in this case consists in isolating the region normally occupied by the ligament, so as to make it inaccessible to the epithelium. This operation can be performed with a biocompatible material implanted in the tissues. The object of the present invention is to describe such a material.

Two types of product are currently known to be used for the purpose of this guided tissue regeneration.

Firstly, the expanded polytetrafluoroethylene membranes marketed under the trademark Gore-Tex® are known, which are not resorbable. These have the advantage of remaining intact throughout the time for which they are implanted, and thereby perfectly fulfil the barrier function they have to perform.

However, they cannot be left in place indefinitely and require two surgical interventions, namely one to insert the material and a second, six to eight weeks later, to remove it once the regeneration phenomenon has been initiated.

On the other hand, resorbable membranes, composed of collagen or other polymers such as polyglycolates, do not require an intervention for removal since they are eliminated by resorption.

Their resorption time is relatively short, however, and they do not always remain intact for long enough to initiate sufficient regeneration.

One object of the present invention is therefore to provide a novel membrane material for guided tissue regeneration which is suturable, biocompatible and slow-resorbing.

A further object of the present invention is to provide a special process for the manufacture of the base material of such membranes.

The present invention makes it possible for the first time to solve this technical problem in a simple, reliable and inexpensive manner which can be used on the industrial and medical scale.

Thus, according to a first feature, the present invention provides a use of collagen crosslinked with a crosslinking agent for the manufacture of a suturable, biocompatible slow-resorbing membrane, preferably for guided tissue regeneration, said membrane either comprising crosslinked collagen from a starting colla-

gen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

In one variant, the degree of crosslinking is such as to increase the denaturation temperature of the collagen by at least 15°C, preferably at least 20°C, compared with native collagen.

The crosslinking agent can be selected from any of the known collagen crosslinking agents. For example, it can be an aldehyde such as a dialdehyde, in particular glutaraldehyde. Preferably, however, the crosslinking agent consists of diphenylphosphoryl azide (abbreviated to DPPA). In contrast to most of the other crosslinking agents, DPPA induces crosslinking and does not bind to the material.

The crosslinking process itself is well known to those skilled in the art. For a DPPA crosslinking process, reference may be made to an earlier patent application in the name of the Applicant, published under no. FR-A-2 645 870, which is incorporated here by way of reference.

The collagen used can be native collagen, in particular of type I or type III.

In one particular variant, it is also possible to use atelocollagen, although this is less preferable.

In another advantageous variant, the above-mentioned mixed membrane is made porous to have a sponge-like appearance, having been prepared by a step involving the lyophilization of a starting gel formed by a collagen or atelocollagen/glycosaminoglycan mixture.

According to a second feature, the present

invention also covers a suturable, biocompatible slow-resorbing membrane comprising collagen crosslinked with a crosslinking agent, preferably for guided tissue generation, said membrane either comprising a crosslinked collagen from a starting collagen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

In one variant, the degree of crosslinking is such as to increase the denaturation temperature of the crosslinked collagen by at least 15°C, preferably at least 20°C, compared with native collagen. The preferred crosslinking agent is diphenylphosphoryl azide, abbreviated to DPPA.

In one variant, the collagen is atelocollagen.

In one advantageous variant, the collagen is a native collagen of type I or type III.

In another variant, the collagen or atelocollagen is mixed with a glycosaminoglycan before the whole is crosslinked with the above-mentioned crosslinking agent.

In another variant of the above-mentioned mixed membrane, the latter is porous, having been prepared in particular by a step involving the lyophilization of a starting gel of a collagen or atelocollagen/glycosaminoglycan mixture.

In another variant, this mixed membrane comprises a sponge produced from a mixture native collagen and a glycosaminoglycan, in particular chondroitin 4-sulfate, onto which a gel of native collagen is poured. Advantageously, the sponge has been compressed under pressure, in particular under a pressure of 150 bar,

before the gel is poured on.

Glycosaminoglycans which can advantageously be used within the framework of the present invention are a structural glycosaminoglycan, in particular hyaluronic acid, chondroitin 4-sulfate, chondroitin 6-sulfate, dermatan sulfate, heparan sulfate, keratan sulfate and heparin and its derivatives, in particular heparins with a low molecular weight of between about 2000 and about 10,000.

The proportion of glycosaminoglycans relative to the collagen or atelocollagen is preferably between 18 and 25%.

The glycosaminoglycan and the collagen or atelocollagen are mixed in solution form. For example, the glycosaminoglycan is in the form of an aqueous solution of glycosaminoglycans containing from 0.5 to 4% by weight, more particularly from 0.5 to 2% by weight and preferably about 1% of glycosaminoglycans. Likewise, the collagen or atelocollagen can be in the form of an aqueous solution having a concentration of between 0.5 and 2% by weight, preferably about 1% by weight, of collagen or atelocollagen. The solution of collagen or atelocollagen can be prepared according to the invention by dissolving collagen or atelocollagen fibers in a slightly acidic aqueous solution, in particular a 0.1 M aqueous solution of acetic acid.

Provision can be made to bring the mixture of collagen or atelocollagen and glycosaminoglycans to a pH close to neutrality and in particular to a pH of between 6.5 and 8. An aqueous solution of sodium hydroxide can be used for this purpose.

According to a third feature, the present invention relates to a specific process for the preparation of the starting collagen. This process is independently patentable and constitutes an independent

invention.

This process comprises the preparation of a collagen gel wherein this gel is coagulated with a coagulating agent comprising an ammoniacal solution preferably having a dehydrating effect.

In one advantageous embodiment of this coagulation process, the ammoniacal solution is an organic ammoniacal solution using acetone as the dehydrating agent. In fact, a synergistic effect is observed with the combination acetone/aqueous ammonia for coagulating the gel and removing the water present in the gel.

The ratio acetone/aqueous ammonia is preferably between 50/50 and 80/20 by volume and particularly preferably 70/30 by volume.

In one advantageous variant, when the amounts of gel to be coagulated are relatively large, the coagulating solution is renewed during coagulation.

In one particular variant, the gel is run through a die of appropriate shape and cross-section to produce a coagulated gel in the appropriate form. If the cross-section of the die is rectangular, a film is obtained; this will subsequently form the membrane.

The coagulated gel obtained can then be crosslinked with the above-mentioned crosslinking agent.

The invention further relates to a process for the manufacture of a suturable, biocompatible slow-resorbing mixed membrane comprising crosslinked collagen, preferably for guided tissue regeneration, which comprises first preparing a collagen sponge and then pouring a collagen gel onto it, and crosslinking the whole with a crosslinking agent, in particular diphenylphosphoryl azide. Advantageously, the collagen sponge comprises a mixture of collagen and a mucopolysaccharide, in particular chondroitin 4-sulfate.

Other variants of the process are also possible

in the context of the foregoing features of the invention. In particular, the collagen can be native collagen, especially of type I or type III, or else it can in practice be atelocollagen, *i.e.* collagen from which the telopeptides have been removed. Moreover, the collagen can be mixed with a glycosaminoglycan.

Thus it is seen that the invention affords all the decisive technical advantages referred to above, as well as the technical advantages which will become apparent to those skilled in the art on the basis of the following explanatory description of the invention referring to two currently preferred embodiments of the invention, which are given simply by way of illustration and cannot therefore in any way limit the scope of the invention. The percentages are given by weight in the Examples, unless indicated otherwise.

Example 1

Preparation of a crosslinked simple collagen membrane

A - Extraction of the native collagen and preparation of the gel:

A gel is prepared from calf skins which have first been washed and depilated with a lime/sulfide mixture (lime: 4%, sodium sulfide: 3%).

It is then unlimed in a bath containing ammonium chloride (2%) and sodium metabisulfite (0.5%). It is then neutralized, after which the salts are removed by two washes with water. It is subsequently ground and then washed with phosphate buffer of pH 7.8 (potassium dihydrogen phosphate 0.78 g/l and disodium monohydrogen phosphate 21.7 g/l). The phosphate is then removed by two successive washes with softened water.

The ground material is then acidified with a 10% solution of acetic acid, the amount of acetic acid being 5% relative to the collagen. The ground material

is then malaxated to give a homogeneous paste. This paste is then diluted to give a gel having a concentration of 0.75% of native collagen.

B - Preparation of the film

The gel obtained is degassed under vacuum and then run into a coagulating bath through a rectangular die whose cross-section has a height of 0.5 mm. The coagulating solution is an acetone/aqueous ammonia mixture (70/30 v/v), which is renewed for every 250 ml of gel.

The film obtained is then dried in air at room temperature on a plastic polytetrafluoroethylene support. When dry, the film is easily detached from its support.

C - Crosslinking of the film

The film is then placed for 24 h at 4°C in a solution of dimethylformamide (DMF) containing 0.5% of diphenylphosphoryl azide (DPPA), the concentration being expressed by volume. The DPPA is removed from the membrane by rinsing in a borate buffer solution of pH 8.9 (sodium tetraborate 0.04 M, boric acid 0.04 M).

The membrane is subsequently incubated for 15 h in the borate buffer solution of pH 8.9 and then rinsed 5 times with deionized water before being placed in a 10% solution of glycerol.

It is then dried in air and sterilized with γ radiation at a dose of 25 kGy (kilogray). The initial and final temperatures of denaturation of the collagen of this membrane are 64 and 80°C respectively.

Example 2

Preparation of a mixed membrane of crosslinked collagen/glycosaminoglycan

A - Extraction of the native collagen and preparation of the gel

A gel is prepared from calf skins which have first been washed and depilated with a lime/sulfide mixture (lime: 4%, sodium sulfide: 3%).

It is then unlimed in a bath containing ammonium chloride (2%) and sodium metabisulfite (0.5%). It is then neutralized, after which the salts are removed by two washes with water. It is subsequently ground and then washed with phosphate buffer of pH 7.8 (potassium dihydrogen phosphate 0.78 g/l and disodium monohydrogen phosphate 21.7 g/l). The phosphate is then removed by two successive washes with softened water.

The ground material is then acidified with a 10% solution of acetic acid, the amount of acetic acid being 5% relative to the collagen. The ground material is then malaxated to give a homogeneous paste. This paste is then diluted to give a gel having a concentration of 0.75% of native collagen.

B - Preparation of the chondroitin 4-sulfate

Lamb's nasal septa from which the muscular and adipose tissues have been removed are chopped and ground by extrusion through a grid having 4 mm holes; the ground material is placed for 24 h at a temperature of 6°C in a potassium chloride buffer (KCl 11.8 g/l, cysteine 78.8 mg/l, EDTA 180 mg/l) containing 1% of "MERCK" papain, the proportion being 130 g of ground material per 1 of buffer.

The supernatant is separated from the residue by continuous centrifugation in a centrifuge rotating at 4000 rpm. 10 g/l of trichloroacetic acid are then

added to the supernatant. The precipitate is removed by continuous centrifugation according to the above technique. The supernatant is neutralized with sodium hydroxide pellets. The mixture is then dialyzed against sterile deionized water using gut with a cut-off threshold of between 6000 and 8000 daltons. The dialyzed solution is lyophilized. The chondroitin 4-sulfate is obtained in the dry state.

C - Preparation of the collagen/chondroitin 4-sulfate sponge

1.87 g of chondroitin 4-sulfate are added to 1 l of 0.75% collagen gel. After neutralization, the mixture is stirred and then lyophilized. The sponge obtained is compressed for 15 s under a pressure of 150 bar.

D - Preparation of the mixed membrane

The 1% collagen gel is run onto the compressed sponge through a die whose cross-section has a height of 0.3 cm. 10 ml of gel are deposited on 35 cm^2 of sponge. The resulting membrane is dried in the open air.

E - Chemical crosslinking of the membrane

The dried membrane is incubated for 24 h at 4°C in a solution of DMF containing 0.5% of DPPA, the concentration being expressed by volume. The DPPA is removed from the membrane by rinsing in a borate buffer solution of pH 8.9 (sodium tetraborate 0.04 M, boric acid 0.04 M). The membrane is subsequently incubated for 15 h in the borate buffer solution of pH 8.9 and then rinsed 5 times with deionized water before being placed in a 10% aqueous solution of glycerol.

The membrane is then dried in air and steri-

lized with γ radiation at a dose of 25 kGy (kilogray). The initial and final temperatures of denaturation of the collagen of this membrane are 60 and 85°C respectively.

The membranes according to the invention can be used as a material for guided tissue regeneration, preferably in dental surgery, for example for filling periodontal pockets, raising maxillo-mandibular ridges or regenerating bone around an implant.

Periodontal pockets are deepenings of the gingival sulcus resulting from bacterial attack of the tissues supporting the tooth.

They are characterized by a loss of the bone substance which is normally present around the root of the tooth and which serves to support it on the jaw.

To use the collagen membrane in this case, the practitioner creates a full thickness flap to expose the damaged bone. He applies the membrane to the bone so as to cover the damage completely and overlap the crown slightly. He finally closes the flap by suturing it so as to leave the membrane overlapping very slightly in the sulcus.

The intervention can also be performed with the concomitant use of biomaterials and bone filling. This technique makes it possible to repair the damaged tissues in 4 to 8 months.

The removal of a tooth from a buccal region is often accompanied by large losses of bone. The surgeon can make good these losses by applying the membrane to the bone so as to cover and overlap the lost bone, taking care to ensure that the space to be reconstructed between the membrane and the bone has the desired shape for reconstruction and, if necessary, that this shape is maintained by using, underneath the membrane, a material which is compatible with the new bone

growth. Finally, he carefully closes the flap to achieve reconstruction in 4 to 8 months.

The surgical implantation of biocompatible artificial metal roots or dental implants in the bone of toothless jaws is a widely used technique in dental surgery.

It often happens that these implants are inserted under conditions which do not allow them to be in contact with the bone over their entire radicular surface, said bone being missing at certain points.

Once again, the use of collagen membranes will enable the surgeon to repair the damaged bone contiguous to the implant.

In this case he will simply use a membrane to cover the region of bone where the implant is inserted, before closing the flap created at the start of the intervention, to give perfect integration of the implant with the bone in 3 to 6 months.

The present invention covers all the means which consist of technical equivalents of the means described and the various combinations thereof.

Furthermore, the invention covers any characteristic which appears to be novel in relation to any state of the art and which results from the foregoing description taken as a whole.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of collagen crosslinked with a crosslinking agent for the manufacture of a suturable, biocompatible slow-resorbing membrane, preferably for guided tissue regeneration, said membrane either comprising crosslinked collagen from a starting collagen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

2. Use according to claim 1 wherein the collagen is native collagen.

3. Use according to claim 2 wherein the collagen is of type I or type III.

4. Use according to claim 1 wherein the collagen is atelocollagen.

5. Use according to any one of claims 1 to 4 wherein the degree of crosslinking is such as to increase the denaturation temperature of the crosslinked collagen by at least 15°C, compared with native collagen.

6. Use according to claim 5, wherein the degree of crosslinking is such as to increase the denaturation temperature of the crosslinked collagen by at least 20°C, compared with native collagen.

7. Use according to any one of claims 1 to 6 wherein the crosslinking agent is diphenylphosphoryl azide, abbreviated to DPPA.

8. A suturable, biocompatible slow-resorbing membrane,

preferably for guided tissue regeneration comprising collagen crosslinked with a crosslinking agent, said membrane either comprising a crosslinked collagen from a starting collagen in the coagulated state produced by coagulating a collagen gel with a coagulating agent, or being in the form of a mixed membrane comprising a sponge of a collagen or atelocollagen/glycosaminoglycan mixture onto which a collagen gel has been poured before the whole is crosslinked.

9. A membrane according to claim 8 wherein the collagen is as defined in one of claims 2 to 7.

10. A membrane according to claim 8 or claim 9 which is a mixed membrane comprising a sponge produced from a mixture of native collagen and a glycosaminoglycan, onto which a gel of native collagen is poured.

11. A membrane according to claim 10 wherein the glycosaminoglycan is chondroitin 4-sulfate.

12. A membrane according to claim 10 or claim 11 wherein the sponge has been compressed under pressure before the gel is poured on.

13. A membrane according to claim 12 wherein the sponge has been compressed under a pressure of 150 bar before the gel is poured on.

14. A process for the coagulation of collagen for the preparation of coagulated collagen according to any one of claims 1 to 7, which comprises coagulating a collagen gel with a coagulating agent comprising an ammoniacal solution.

15. A process according to claim 14 wherein the ammoniacal solution has a dehydrating effect.

16. A process according to claim 15 wherein the ammoniacal

solution is an organic ammoniacal solution comprising acetone as a solvent.

17. A process according to claim 16 wherein the ratio acetone/ammonia is between 50/50 and 80/20 by volume.

18. A process according to claim 17 wherein the ratio acetone/ammonia is about 70/30.

19. A process according to any one of claims 14 to 18 wherein, when the amounts of gel to be coagulated are too large, the coagulating solution is renewed during coagulation.

20. A process according to any one of claims 14 to 19 wherein the gel is run through a die of appropriate cross-section and shape so as to give a film.

21. A process according to claim 20 wherein the die is of rectangular cross-section.

22. A process for the manufacture of a suturable, biocompatible slow-resorbing mixed membrane comprising crosslinked collagen, preferably for guided tissue regeneration, which comprises first preparing a sponge of a collagen or atelocollagen/glycosaminoglycan mixture and then pouring a collagen gel onto it, and crosslinking the whole with a crosslinking agent.

23. A process according to claim 22 wherein the crosslinking agent is diphenylphosphoryl azide.

24. A process according to claim 22 or claim 23 wherein the collagen sponge comprises a mixture of native collagen and a glycosaminoglycan.

25. A process according to claim 24 wherein the

glycosaminoglycan is chondroitin 4-sulfate.

26. A process according to any one of claims 22 to 24 wherein the sponge is compressed under pressure before the collagen gel is poured on.

27. A process according to claim 26 wherein the sponge is compressed under a pressure of 150 bar before the collagen gel is poured on.

Dated this 23rd day of March, 1995
COLETICA
by DAVIES COLLISON CAVE
Patent Attorneys for the Applicant(s).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 92/00750

A. CLASSIFICATION OF SUBJECT MATTER

IPC5 A61L31/00; A61L27/00
According to International Patent Classificati n (IPC) r to both nati nal classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
X	WO,A,9 013 302 (BRIGHAM AND WOMEN'S HOSPITAL) 15 November 1990	1,8
Y	see page 5, line 3 - line 8	3-7,9,11-13
X	EP,A,0 331 786 (CHEMOKOL) 13 September 1989 see column 7; example 7 see claims 1,7,8	1,8
Y	EP,A,0 052 288 (HEYL) 26 May 1982 see claims 1,4,14	3
Y	EP,A,0 187 014 (COLLAGEN) 9 July 1986 see page 6, line 31; claim 8	4

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☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date f mailing of the international search report
14 October 1992 (14.10.92)	20 November 1992 (20.11.92)
Name and mailing address of the ISA/ EUROPEAN PATENT OFFICE Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 92/00750

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation f document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 280 954 (YANNAS I.V.) 28 July 1981 see column 8, line 60 - line 62 see column 21, line 36 - line 44 see column 22, line 46 - line 47	5,7
Y	WO,A,9 012 055 (BIOETICA) 18 October 1990 cited in the application see page 1, line 12 - line 15 see page 4, line 19 - line 21 see page 6; example 2 see page 9; table I see claims 9,12	6,7,9
Y	EP,A,0 156 740 (CENTRE TECHNIQUE DU CUIR) 2 October 1985 see claim 1	11-13

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. FR 9200750 SA 63240

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/10/92
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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RAPPORT DE RECHERCHE INTERNATIONALE

PCT/FR 92/00750

Demande Internationale No

I. CLASSEMENT DE L'INVENTION (si plusieurs symboles de classification sont applicables, les indiquer tous) [7]

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

CIB 5 A61L31/00; A61L27/00

II. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée[8]

Système de classification	Symboles de classification
CIB 5	A61L

Documentation consultée autre que la documentation minimale dans la mesure où de tels documents font partie des domaines sur lesquels la recherche a porté[9]

III. DOCUMENTS CONSIDERES COMME PERTINENTS[10]

Catégorie *	Identification des documents cités, avec indication, si nécessaire,[12] des passages pertinents[13]	No. des revendications visées [14]
X	WO,A,9 013 302 (BRIGHAM AND WOMEN'S HOSPITAL) 15 Novembre 1990	1,8
Y	voir page 5, ligne 3 - ligne 8	3-7,9, 11-13
X	EP,A,0 331 786 (CHEMOKOL) 13 Septembre 1989 voir colonne 7; exemple 7 voir revendications 1,7,8	1,8
Y	EP,A,0 052 288 (HEYL) 26 Mai 1982 voir revendications 1,4,14	3
Y	EP,A,0 187 014 (COLLAGEN) 9 Juillet 1986 voir page 6, ligne 31; revendication 8	4

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* Catégories spéciales de documents citées:[11]

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

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"T" document ultérieur publié postérieurement à la date de dépôt international ou à la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier.

"&" document qui fait partie de la même famille de brevets

IV. CERTIFICATION

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
14 OCTOBRE 1992	20. 11. 92
Administration chargée de la recherche internationale	**Signature du fonctionnaire autorisé**
FFICE EUR PEEN DES BREVETS	Mme Dagmar FRANK

Formulaire PCT/ISA/210 (deuxième feuille) (Janvier 1985)

III. DOCUMENTS CONSIDERES COMME PERTINENTS [14] (SUITE DES RENSEIGNEMENTS INDIQUES SUR LA DEUXIEME FEUILLE)

Catégorie *	Identification des documents cités, [16] avec indication, si nécessaire des passages pertinents [17]	No. des revendications visées [18]
Y	US,A,4 280 954 (YANNAS I.V.) 28 Juillet 1981 voir colonne 8, ligne 60 - ligne 62 voir colonne 21, ligne 36 - ligne 44 voir colonne 22, ligne 46 - ligne 47	5,7
Y	WO,A,9 012 055 (BIOETICA) 18 Octobre 1990 cité dans la demande voir page 1, ligne 12 - ligne 15 voir page 4, ligne 19 - ligne 21 voir page 6; exemple 2 voir page 9; tableau I voir revendications 9,12	6,7,9
Y	EP,A,0 156 740 (CENTRE TECHNIQUE DU CUIR) 2 Octobre 1985 voir revendication 1	11-13

ANNEXE AU RAPPORT DE RECHERCHE INTERNATIONALE RELATIF A LA DEMANDE INTERNATIONALE NO.

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Lesdits membres sont contenus au fichier informatique de l'Office européen des brevets à la date du
Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office européen des brevets. 14/10/92

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